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Relationship Among Viral Load Outcomes in HIV Treatment Interruption Trials

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Abstract

Viral load (VL) rebound timing and set point were analyzed in 235 participants undergoing analytic treatment interruption (ATI) in 6 ACTG studies. There was no significant association between rebound timing and ATI VL set point for those who rebounded ≤12 weeks. VL set points were lower in participants with rebound >12 weeks ($p<0.001$) and participants treated during early infection ($p<0.001$). Pre-ART VL correlated with set point, though 68% of participants had a set point lower than pre-ART VL. These results illustrate complex relationships between post-ATI virologic outcomes and the potential presence of biological factors mediating rebound timing and set point.

Keywords

HIV; treatment interruption; set point; viral rebound; outcome

Introduction

Antiretroviral Therapy (ART) is effective at controlling HIV, and can suppress the plasma viral load (VL) below levels of detection. However, when treatment is stopped, the virus will almost inevitably rebound. The search continues for an HIV "functional cure"—an

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intervention that allows for sustained, ART-free virologic remission. Clinical efficacy of such interventions will need to be tested in analytic treatment interruption (ATI) trials. However, the interpretation of ATI studies has been complicated by the use of varying virologic outcome measures, making comparisons and relative evaluations between ATI trials difficult.

VL set point has historically been the most commonly used virologic endpoint in ATI trials,[1-3] but recent studies have also begun evaluating the timing of viral rebound in a study design that has been termed an intensely monitored antiretroviral pause (IMAP).[4-7] However, little is known about the relationship between these two virologic outcomes. In addition, it has been postulated that pre-ART VL and ATI VL set point are nearly identical[1] and the difference between pre-ART VL and ATI VL set point has been used as a marker of therapeutic efficacy in previous studies.[1, 3, 8-10] Using a pooled dataset of 6 AIDS Clinical Trials Group (ACTG) ATI studies, we performed an in-depth characterization of ATI VL endpoints.

Methods

Study Population

Participants in 6 ACTG ATI studies (ACTG 371,[11] A5024,[12] A5068,[13] A5170,[14] A5187,[15] and A5197[2]) were included if they were on suppressive ART, received no recent immunologic interventions (e.g., therapeutic vaccination), and had HIV-1 RNA <50 copies/mL at the time of ATI. Protocols ACTG 371[11] and A5187[15] enrolled participants treated within 6 months of infection. Participants in ACTG 371 were treated for 52 weeks prior to the ATI; those in A5187 had to be on a stable ART with HIV-1 RNA <50 copies/mL for at least 6 months prior to enrollment.

Statistical analysis

The time to viral rebound was defined as the week at which there was a confirmed HIV RNA ≥200 copies/mL. VL set point was defined as the mean viral load between weeks 12 and 16. Associations between set point and timing of viral rebound were analyzed using Spearman correlation, Kruskal-Wallis, Mann-Whitney, and chi-square tests. The correlation of pre-ART VL vs. ATI set points was analyzed by Spearman correlation and Wilcoxon signed-rank test. We also performed a sensitivity analysis of all participants who underwent ATI in which those who discontinued the ATI prior to week 12 were assigned a set point viral load equal to their last known viral load.

Results

Participants

Of the 235 participants, 91% were male, 71% were white, 14% Hispanic, 13% black, and 3% other. Participants in this study had a median age of 41 years. 66% were treated during chronic infection and 34% during early infection. The median CD4+ cell count at the start of ATI was 827 cells/mm^3. Participants treated during chronic infection had a median (Q1, Q3) of 5.1 (3.2, 6.5) years on ART.

HIV Rebound Timing and Set Point

For participants who had HIV rebound at or before week 12, there were no significant association between timing of viral rebound and the VL set point (Fig. 1A and 1B). However, participants who rebounded after week 12 also showed much lower set points (rebound ≤12 (N=180) vs. >12 weeks (N=14): median 4.1 vs. 1.9 $\log_{10}$ HIV RNA copies/mL, P<0.001). Lower ATI set points were more frequent among those with delayed viral rebound. Specifically, 10 of 154 (6.5%) participants who rebounded within the first 4 weeks had VL set points <1,000 RNA copies/mL, as compared to 7 of 57 (12.3%) who rebounded in weeks 5-8, 1 of 10 (10%) who rebounded in weeks 9-12, and 11 of 14 (79%) of those who rebounded after week 12 (X^2 P<0.001, Supplemental Figure 1A). We also performed a sensitivity analysis in which the last available VL measurement was used for 41 participants who did not reach week 12 of the ATI. The results were largely unchanged, reaffirming the original findings.

Participants treated during early infection were found to have a lower VL set point (early vs. chronic: median 3.5 vs. 4.2 $\log_{10}$ HIV RNA copies/mL, p<0.001, Fig. 1C). No significant difference was observed in VL set point between those on NNRTI or PI-based ART regimens.

Association Between Pre-ART VL and ATI VL Endpoints

In the 96 chronically treated participants who had both pre-ART VL and ATI set point data, there was a significant correlation between these two measures (Spearman r=0.39, p<0.001, Fig. 2A). The VL set point tended to be lower than the pre-ART VL with a median 2-fold decrease by patient (Q1, Q3: 5-fold decrease, 1.8-fold increase, Fig. 2B). Furthermore, 68% of participants had VL set points lower than pre-ART levels. The results were largely unchanged in the sensitivity analysis using the last available VL for participants who did not reach ATI week 12 (pre-ART VL vs. ATI VL set point Spearman r=0.40, P<0.001; median 2 fold decrease; and 68% of participants with lower VL set point vs. Pre-ART VL). No significant association was found between pre-ART VL and time to viral rebound, although there were relatively few participants in the viral rebound >12 week group with available pre-ART VL data.

Discussion

HIV treatment interruption trials are expected to play a key role in evaluating the efficacy of interventions aimed at achieving sustained HIV remission. The comparison of interventions between ATI studies has been hindered by the heterogeneity in virologic outcomes and uncertainty in how to interpret trials without a placebo control arm. In this study, we found that the timing of viral rebound and ATI VL set point were largely independent when viral rebound occurred at or before ATI week 12. However, those who rebounded after week 12 were found to have significantly lower ATI VL set point. In addition, participants treated during early HIV infection were found to have lower ATI VL set point—a finding that is consistent with other studies that show favorable rebound kinetics for those treated during early stages of infection.[16, 17] Finally, while we observed a correlation between pre-ART VL and ATI VL set point, the VL set point was frequently lower than the pre-ART VL with a wide range in possible outcomes.

Traditionally, ATI studies have used VL set point as a common endpoint for therapeutic efficacy. However, given the concern for prolonged participant exposure to rebound viremia, an alternative treatment interruption study design termed the intensively monitored antiretroviral pause (IMAP) has gained in popularity.[4] This approach uses the time to viral rebound as the primary endpoint, which may entail less risk to the participants and act as a more clinically relevant outcome. However, little is known about the relationship between these two primary study endpoints. The results of this study show that for individuals who rebound at or before ATI week 12, there is no significant correlation between the timing of viral rebound and the VL set point. Thus, interventions that confer a modest delay in viral rebound timing may not necessarily have a significant effect on VL set point. Interestingly, we found that those who rebounded after week 12 had significantly lower VL set points, suggesting the potential presence of immunologic and/or virologic factors in this subset of participants that can both delay viral rebound and suppress the VL set point. It is important to note that even drastically delayed viral rebound are not always associated with lower set point, especially in those whose immune system are relatively naive to HIV. This was seen in the two Boston patients who underwent allogeneic stem cell transplantation with both delayed viral rebound timing and high levels of VL after ATI.[6]

A previous study observed that the pre-ART viral load appeared to be “virtually identical” to the ATI VL set point.[1] This observation would suggest that a change in VL between the ATI set point and pre-ART VL could be used as a study endpoint and may especially be useful in those studies without a control arm. In fact, lower ATI set point compared to pre-ART VL has been presented as evidence of therapeutic efficacy in several ATI studies.[8-10] However, our results show that in more than two-thirds of participants, the ATI VL set point was lower than the pre-ART VL. The median value was a 2-fold lower VL set point with the 25th and 5th percentiles encompassing a 5-fold and 50-fold lower VL set points compared to pre-ART VL, respectively. There are a number of possible causes for this tendency for VL set point to be lower. These include a smaller HIV reservoir after sustained ART[18, 19], immune reconstitution after ART,[20] or that 16 weeks of ATI is insufficient time to allow the VL to return to pre-ART levels.[21] The overall lower ATI VL set point and wide range of possible outcomes suggest that the comparison with pre-ART VL should be interpreted cautiously and may be a less accurate reflection of therapeutic efficacy than previously thought.

One notable limitation of this analysis is that a subset of individuals who initiated ATI stopped the treatment interruption phase of the studies prior to ATI week 12. These individuals could have potentially reached alternate criteria for ART reinitiation, including rapid viral rebound, biasing the analysis to those with lower VL set points. Therefore, we performed sensitivity analysis with a carry-forward of the last recorded VLs as the VL set point for participants who did not reach ATI week 12. The results were comparable to the primary analysis, reaffirming the original conclusions. Another limitation of the analysis is that only a subset of chronically infected participants (N=96) have available pre-ART VL. However, the numbers were sufficiently substantial to demonstrate the wide variance of VL set point in relation to pre-ART VL and the risks associated with the use of the comparison as an indicator of therapeutic efficacy.

HIV ATI trials represent the most conclusive strategy for evaluating the efficacy of HIV curative therapies. A detailed understanding of ATI VL endpoints is needed for the optimal design and interpretation of these trials. Our results revealed the complex relationship between several key virologic factors, including pre-ART VL, viral rebound timing, and VL set point. The results underscore the difficulties in interpreting uncontrolled ATI studies. In addition, the association of delayed viral rebound with suppressed VL set point suggests the presence of key immunologic and/or viral factors mediating both of these outcomes and this observation deserves further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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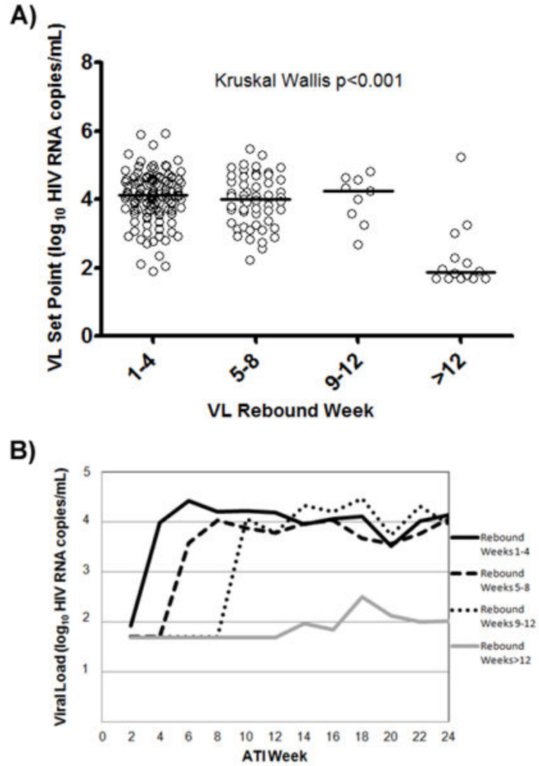


Rebound 1-4 (N)	100	154	88	125	65	100	40	87	40	23	23	58
Rebound 5-8 (N)	32	43	35	50	31	42	17	41	15	13	6	29
Rebound 9-12 (N)	4	6	5	6	6	6	7	6	5	1	2	4
Rebound 13+ (N)	9	14	6	14	7	12	3	10	4	8	4	10

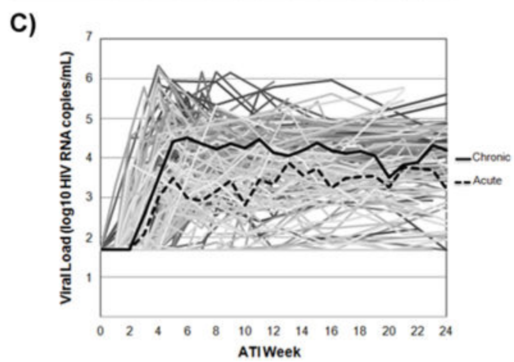
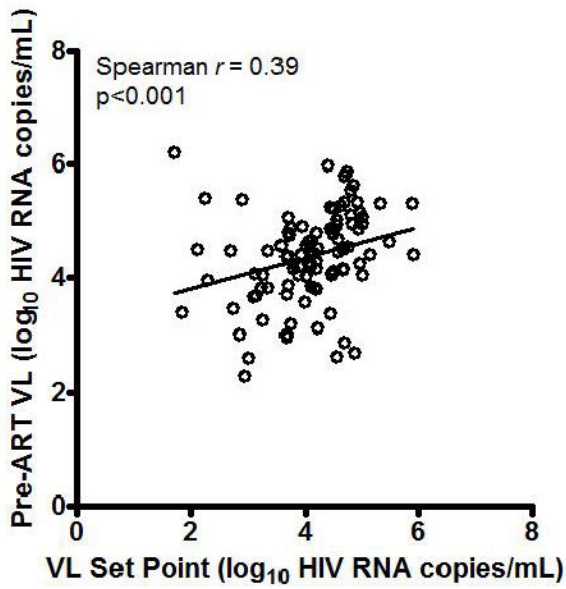


Figure 1. Analysis of post-ATI VL endpoints

A) VL set points and median by rebound category. B) Median VLs categorized by viral rebound week using a two week window for each time point with the number of observations per category per time point listed below. C) VLs for all patients shown, with median VLs of chronic and acutely-treated participants in solid and dashed lines, respectively.

A)



B)

Percentile	Fold Change
Minimum	$3.13*10^{-5}$
5%	0.02
25%	0.19
50%	0.50
68%	1.00
75%	1.85
95%	11.87
Maximum	148.72

Figure 2. Relationship of pre-ART Viral Load and Post-ATI Set Point

A) Plot of pre-ART VL vs. set point for 95 chronically infected patients for whom data were available. B) Percentile data for fold change of ATI VL Set Point to Pre-ART VL (non $\log_{10}$ transformed). Fold change represents post-ATI set point divided by pre-ART viral load.